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Final Report on Methylene Derivatives as Reaction Intermediates

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by Jack Hine

Nontechnical Information

Mr. Robert L. McDaniel was a graduate research assistant on the project from its inception (June 27, 1962) until the end of October, 1963. He was a candidate for an M. S. degree but dropped out of school without completing the requirements for the degree. Mr. Roy B. Duke was a graduate research assistant from November, 1963, until the project terminated in June, 1965. It is anticipated that Mr. Duke will complete the requirements for the Ph. D. in organic chemistry at Georgia Tech during 1966.

Dr. Benjamin F. Plummer was a postdoctoral research fellow on the project from November, 1962, until September, 1963, when he accepted a faculty position at South Dakota State University. The second postdoctoral research fellow was Dr. Martin Isacs, who worked from October, 1963, until September, 1964, when he accepted a postdoctorate appointment at Brown University. The last postdoctoral fellow was Dr. James O. Schreck who worked from September, 1964 until the project terminated in June, 1965, after which he continued research under other sponsorship at Georgia Tech.

No previous technical reports were produced on this project, and no journal articles have appeared or been submitted. It is anticipated that several journal articles will appear describing research carried out on this project but in some cases additional laboratory work will be necessary, as described in the technical section of this report, before publication is desirable.

Technical Information

Abstract.-- The purpose of this investigation was to learn more about reactions in which methylene and its derivatives are, or have been claimed to be, intermediates.

A study of the mechanism of the reaction of the Simmons-Smith reagent [ICH_2ZnI or $(ICH_2)_2Zn$] with olefins was discontinued when no really good method for analyzing for the reagent could be devised and when work on the problem was published from another laboratory.

A study of the mechanism of the reaction of p-nitrobenzyl halides with strong bases was discontinued when the separation and identification of the reaction products proved to be difficult.

The relative efficiencies with which various phenoxide ions capture difluoromethylene were investigated in order to learn whether the o-hydroxyphenoxide ion is particularly efficient, as it might be if it acts as a bifunctional reagent. No marked increased efficiency of capture by o-hydroxyphenoxide ions is evident from the results obtained.

The reactions of methylene halides with alkali-metal alkoxides were investigated to learn what the reaction conditions are at which the mechanism of displacement of the halogens changes from S_N2 to an α-elimination mechanism. With all the methylene halides studied under all the reaction conditions employed, it was found that, although carbanion formation occurred, it was not an intermediate step in displacement of the halogen by an α-elimination mechanism but instead a rather irrelevant side reaction accompanying the displacement of halogen by an S_N2 mechanism.

The reaction of potassium t-butoxide with dichlorofluoromethane has been found to give an interesting new compound, the t-butyl ester of

di-t-butoxyacetic acid, in addition to cis- and trans-1,2-di-t-butoxy-1,2-difluoroethylene, already reported as products of the analogous reaction of chlorodifluoromethane. Alkoxymethylenes may be intermediates in these reactions.

In other studies relating to alkoxymethylenes, particularly dialkoxymethylenes, a new synthesis for compounds of the type $(RS)_2CHOR$ has been developed, the reactions of propylene glycol with haloforms and bases have been found to give a little propylene, and trimethyl orthoformate has been found to undergo deuterium exchange with deuteromethanol in the presence of an acetate buffer.

Mechanism of Action of the Simmons-Smith Reagent.-- The existing observations concerning the Simmons-Smith reagent[1,2] provided evidence against the hypothesis that the formation of cyclopropane derivatives in certain reactions carried out in the presence of olefins is proof of the intermediate formation of methylene derivatives. To strengthen this evidence a quantitative kinetic investigation was needed, however.[3a] For this reason we attempted to devise a method for analysis for the Simmons-Smith reagent, which is either iodomethylzinc iodide or bis(iodomethyl)zinc. An iodometric titration, an acidimetric titration, a titration for zinc, and a titration for iodide were all worked out and various combinations of these applied to the problem of determining the reagent concentration. In no case, however, did we obtain the reproducibility and assurance that our analytical data actually corresponded to the Simmons-Smith reagent concentration that would be needed for a really reliable kinetic investigation. We could have been content with analyzing simply for the olefin and cyclopropane, but by this time Blanchard and Simmons[4] had completed a kinetic study of this type. Any work of ours would probably not have been an improvement on their investigation and for this reason we abandoned

this part of the project.

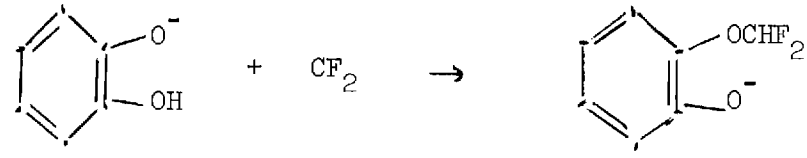
Mechanism of the Reaction of p-Nitrobenzyl Halides with Strong Base.--

Although good evidence exists that the formation of p,p'-dinitrostilbene from p-nitrobenzyl halides and sulfonium salts involves the intermediate formation of p-nitrobenzylidene,[5,6] there are several unusual aspects of the reaction that seemed to make it worth additional study.[3b] One of these aspects, for example, is the remarkable specificity with which the intermediate p-nitrobenzylidene reacts.

The reported observations that the reaction, as measured by the disappearance of base, is second order (first order in p-nitrobenzyl halide and first order in base) and that the reaction in a deuterated solvent is accompanied by deuterium exchange of the reactant were verified. It was also found, however, that in addition to the reported reaction products, cis- and trans-p,p'-dinitrostilbene, and the substitution product, p-nitrobenzyl alcohol or an alkyl p-nitrobenzyl ether, there are other products formed. One of these resembled the trans-dinitrostilbene in that it melted (with decomposition) at around 300° and was relatively insoluble in all common organic solvents at room temperature. It had an ultraviolet absorption maximum at a considerably shorter wave length than the trans-dinitrostilbene, however. Our initial attempts showed that the problem of determining the structure of the compound would make the overall mechanistic study considerably more difficult than had been anticipated. Therefore, this part of the project was abandoned.

Capture of Difluoromethylene by Aryloxide Ions.-- In view of the importance of bifunctional catalysis in many other types of reactions it seemed worthwhile to learn whether dihalomethylene capture could be made more efficient by use of a suitable bifunctional reagent. Inasmuch as there is evidence that the combination of difluoromethylene with certain nucleophilic reagents is accompanied by the simultaneous abstraction of a proton

from the solvent,[3c] it seemed that the capture of difluoromethylene by the o-hydroxyphenoxide ion might involve the simultaneous formation of two new bonds to carbon.



However, from a study of the relative efficiency of various aryloxide anions at capturing difluoromethylene, it appears that the o-hydroxyphenoxide ion is not significantly more efficient than would be expected from its basicity.

Mechanism of the Reaction of Methylene Halides with Alkali-Metal Alkoxides.--

Closs and coworkers have established that the reaction of methylene chloride with alkyllithium compounds involves very largely an α-dehydrochlorination.[3d,7] In the reaction of methylene chloride, bromide, and iodide with dry potassium t-butoxide, Kursanov and coworkers have shown that at least some α-dehydrohalogenation occurs, but this may be anywhere from about 1% to almost 100% of the total reaction.[3d,8] On the other hand, in such nucleophilic substitution reactions as the attack of iodide ions on methylene chloride, most physical organic chemists would probably be surprised if any detectable fraction of the reaction involved α-elimination. Although it seems clear that, as would be expected, the extent of α-elimination tends to increase with the basicity toward hydrogen of the nucleophilic reagent employed, it is not clear just where the principal mechanism for substitution reactions of methylene halides changes from S_N2 to α-elimination. In order to learn more about this we have studied the mechanism of reaction of a number of methylene halides with alkali-metal alkoxides of varying basicity.

Several criteria were used to tell whether the reactions studied

were α-eliminations or S_N2 reactions. The deuterium content of the formals obtained as reaction products when the reactions were carried out in deuterated alcohols as solvent were measured. Reaction by the α-elimination mechanism should necessarily give a deuterated product.

$$CH_2X_2 \xrightarrow{RO^-} H\text{-}C\text{-}X \xrightarrow{ROD} ROCHDX$$

$$ROCHDX \rightarrow (RO)_2CHD \text{ or } (RO)_2CD_2$$

Reaction by the S_N2 mechanism need not necessarily give a deuterated product under these conditions but it may if the starting material undergoes deuterium exchange with the solvent. In the reaction of methylene bromide with sodium methoxide in deuteromethanol, the methylal produced was found to contain no more deuterium than would be expected from the deuterium exchange of the methylene bromide, whose kinetics were also studied. Therefore the formation of the methylal did not consist of α-elimination to any detectable extent. In the presence of isopropoxide ions in isopropyl alcohol and of t-butoxide ions in t-butyl alcohol, the deuterium exchange of all the methylene halides investigated was so much faster than the formation of dialkyl formal that it was not possible to distinguish between the S_N2 and α-elimination mechanisms on the basis of the deuterium content of the reaction product.

Another criterion for determining the reaction mechanism is based on the fact that such known α-elimination reactions as the basic decomposition of chloroform are much faster in the presence of potassium t-butoxide in t-butyl alcohol than in the presence of sodium methoxide in methanol; known S_N2 reactions, such as the Williamson ether synthesis using methyl iodide, are affected to a much smaller extent by the change in reaction conditions from methanolic sodium methoxide to potassium t-butoxide in

t-butyl alcohol. We observed that the rate of the reaction varies with

$$CH_2X_2 + 2RO^- \xrightarrow{ROH} CH_2(OR)_2 + 2X^-$$

the nature of R in a manner much more nearly like that of the analogous reaction of methyl iodide than like that of the analogous reaction of chloroform. We therefore conclude that the formation of dialkyl formals occurs very largely by the S_N2 mechanism.

At present Mr. Roy Duke is preparing a description of this work and that on the capture of difluoromethylene by aryloxide ions for his Ph. D. thesis, which, it is hoped, will provide the basis for two journal articles on these two subjects.

Reaction of Dichlorofluoromethane and Chlorodifluoromethane with Potassium t-Butoxide.-- Cleaver has reported that the reaction of chlorodifluoromethane with potassium t-butoxide yields a mixture of cis- and trans-1,2-di-t-butoxy-1,2-difluoroethylene.[3e,9]

$$2CHClF_2 + 4t\text{-BuOK} \rightarrow t\text{-BuOCF=CFOBu-}t + 2KCl + 2KF$$

This reaction is interesting not only because of the rather unusual nature of the product but also because it may involve the dimerization of t-butoxyfluoromethylene. Although the generation of methylenes as reaction intermediates is becoming rather common, their dimerization to give olefins is not common; p-nitrobenzylidene, for example, is believed to yield p,p'-dinitrostilbene by reaction with an α-chloro-p-nitrobenzyl anion (followed by loss of chloride ion) not by dimerization. If the di-t-butoxydifluoroethylenes are formed from t-butoxyfluoromethylene they should arise from dichlorofluoromethane as readily as from chlorodifluoromethane, if not more so.

Therefore we investigated the reaction of dichlorofluoromethane with

potassium t-butoxide in t-butyl alcohol. We obtained the di-t-butoxydifluoroethylenes, as expected, and also a higher boiling white solid product that melts at about 53°. From its simple n.m.r. spectrum, its infrared spectrum, its elemental analysis, and its mode of formation we have concluded that this product is the t-butyl ester of di-t-butoxyacetic acid. Preliminary experiments seem to show that this ester is not formed in the reaction proper, which is carried out in some cases at temperatures below 30°, but in the work-up, wherein the reaction mixture is heated to about 90° to drive off the solvent. If this is true the reaction mixture at 30° must contain a precursor of the ester. Perhaps careful work at low temperatures would permit the isolation and identification of this precursor.

In the reaction of chlorodifluoromethane with potassium t-butoxide we identified a new product, t-butyl difluoromethyl ether, whose formation we had predicted on the basis of published observations using other alkali-metal alkoxides.[3f,10] Cleaver's report of the formation of the di-t-butoxydifluoroethylenes was confirmed and isobutylene was also found to be a reaction product but no t-butyl di-t-butoxyacetate was found. It is possible, however, that the reaction mixture became acidic during the work-up and the ester, which would be expected to be rather sensitive to acid, was destroyed.

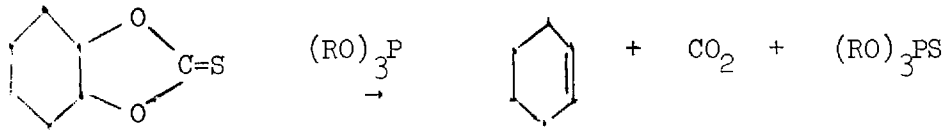
It is hoped that there will be an opportunity for future work in this area. The precursor of t-butyl di-t-butoxyacetate should be sought. It should be established clearly whether the ester is formed from chlorodifluoromethane or not. An investigation of the manner in which changes in the reaction conditions change the relative yields of the various products may provide information on the nature of the reaction mechanism.

The Reaction of $(MeS)_2$ CHOMe with Strong Base.-- In view of the reported observation that trialkylorthothioformates react with potassium amide to give tetrakis(alkylthio)ethylenes,[3g] it seemed of interest to study the reaction of compounds of the type $(RS)_2CHOR$ and $RSCH(OR)_2$ with strong bases. (Trialkylorthoformates have previously been found to be inert to the action of potassium amide and sodium hydride at moderate temperatures, at least.). The following new synthesis was devised for the dithioorthoformates:

$$MeOCHCl_2 + 2MeS^- \rightarrow MeOCH(SMe)_2$$

In reactions with sodium hydride and with potassium amide that were tried, however, the reaction product was found to be either an intractable tar or unchanged starting material.

The Generation of Dialkoxymethylenes.-- Corey and coworkers have found that the treatment of cyclic thionocarbonates derived from 1,2-diols with trialkyl phosphites brings about the formation of olefins,[3h,11] e.g.,

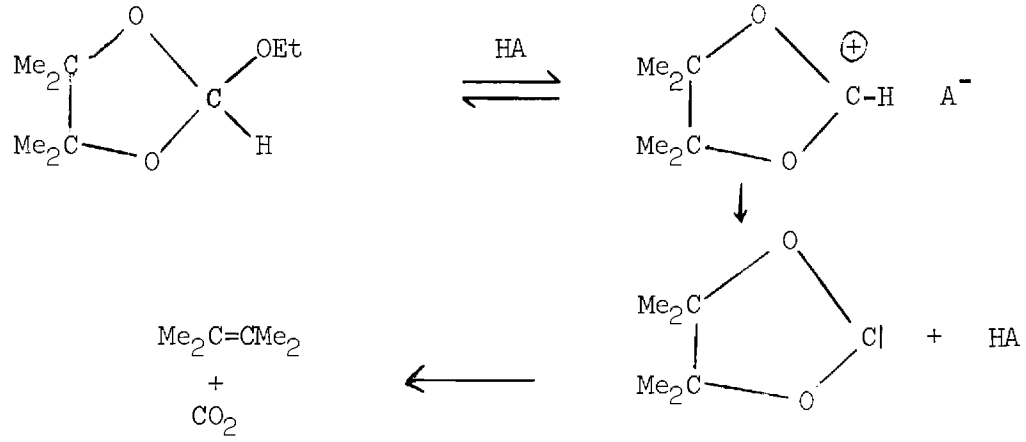


This reaction may involve the formation of a cyclic dialkoxymethylene, which subsequently decomposes to carbon dioxide and olefin, or it may be a concerted process. If the reaction is concerted or if decomposition is invariably the preferred reaction path for the intermediate cyclic dialkoxymethylene, then other reactions that might be expected to lead to such a cyclic dialkoxymethylene would also be expected to yield olefins. The formation of trialkyl orthoformates from haloforms and alkali-metal

alkoxides is a reaction that may involve the intermediate formation of dialkoxymethylenes. However, plausible reaction paths may also be written that do not involve intermediate dialkoxymethylenes. This is one reason why it seemed of interest to study the reaction of the alkali-metal salts of 1,2-diols with haloforms.

In the reaction of chloroform with the sodium salt of propylene glycol in propylene glycol solution, very little propylene is formed in the basic reaction solution at temperatures up to 100°. However, when the reaction in the presence of excess chloroform has been completed and the neutral or slightly acidic reaction mixture is heated to about 160°, large quantities of propylene are evolved.

Very shortly after this observation was made it was explained by the appearance of a paper by Crank and Eastwood.[12] These workers found that when 2-alkoxy-1,3-dioxolanes are heated in the presence of a small amount of a weak acid, olefins and carbon dioxide are formed. They suggested the following reaction mechanism (among others).



If this mechanism is correct, then it might be expected that other orthoformate esters would yield dialkoxymethylenes upon treatment with weak acid. However, with most such esters the dialkoxymethylene formed

would not be capable of decomposition to carbon dioxide and olefin. Therefore the formation of dialkoxymethylene might very well be reversible and hence observable in the form of an exchange reaction by the hydrogen atom attached to the trioxygenated carbon atom. To test this possibility we heated a mixture of trimethyl orthoformate, deuteromethanol, and a little acetic acid and sodium acetate to 190° in an n.m.r. tube. The change in the n.m.r. spectrum gave good evidence for the following exchange reaction:

$$(MeO)_3CH + MeOD \underset{NaOAc}{\overset{DOAc}{\rightleftharpoons}} (MeO)_3CD + MeOH$$

We therefore think that it is quite likely that dimethoxymethylene was an intermediate in the reaction. We hope that further information can be obtained about this reaction by studies of the kinetics and the effect of structure on reactivity.

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10. J. Hine and K. Tanabe, J. Am. Chem. Soc., 79, 2654 (1957); 80, 3002 (1958).

11. E. J. Corey and R. A. E. Winter, ibid., 85, 2677 (1963).

12. G. Crank and F. W. Eastwood, Australian J. Chem., 17, 1392 (1964).